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Superoxide dismutase – applications and relevance to human diseases

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Summary

Reactive oxygen species, such as superoxide radicals, are thought to underlie the pathogenesis of various diseases. Almost 3 to 10% of the oxygen utilized by tissues is converted to its reactive intermediates, which impair the functioning of cells and tissues. Superoxide dismutase (SOD) catalyzes the conversion of single electron reduced species of molecular oxygen to hydrogen peroxide and oxygen. There are several classes of SOD that differ in their metal binding ability, distribution in different cell compartments, and sensitivity to various reagents. Among these, Cu, Zn superoxide dismutase (SOD1) is widely distributed and comprises 90% of the total SOD. This ubiquitous enzyme, which requires Cu and Zn for its activity, has great physiological significance and therapeutic potential. The present review describes the role of SODs, especially Cu, Zn SOD, in several diseases, such as familial amyotrophic lateral sclerosis (FALS), Parkinson's disease, Alzheimer's disease, dengue fever, cancer, Down's syndrome, cataract, and several neurological disorders. Mutations in the SOD1 gene cause a familial form of amyotrophic lateral sclerosis. The mechanism by which mutant SOD1 causes the degeneration of motor neurons is not well understood. Transgenic mice expressing multiple copies of FALS-mutant SOD1s develop an ALS-like motor neuron disease. Vacuolar degeneration of mitochondria has been identified as the main pathological feature associated with motor neuron death and paralysis in several lines of FALS-SOD1 mice. Various observations and conclusions linking mutant SOD1 and FALS are discussed in this review in detail.

key words: **familial amyotrophic lateral sclorosis (FALS) • Parkinson's disease • Alzheimer's disease • oxidative damage • superoxide radical • Cu, Zn SOD**

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BACKGROUND

Superoxide dismutase (SOD) is an enzyme catalyzing the disproportion of superoxide radicals to dioxygen and hydrogen peroxide, according to the following formulae:

$$M^{3+} + O_2^- \rightarrow M^{2+} + O_2$$

$$M^{2+} + O_2^- + 2H^+ \rightarrow M^{3+} + H_2O_2$$

SOD is found abundantly in many organisms, from microorganisms to plants and animals, since superoxide radicals are toxic to living cells, oxidizing and degrading biologically important molecules, such as lipids and proteins [1–4]. Several types of SOD, have been reported, based on the requirement of the metal species at the active site:

(a) copper-and zinc-containing superoxide dismutase (Cu, Zn SOD)

(b) Iron-containing superoxide dismutase (Fe SOD)

(c) manganese-containing superoxide dismutase (Mn SOD) [5-7].

In addition, Ni-containing superoxide dismutase has recently been found in *Streptomyces griseus* and *S. coelicolor* [8–10].

Cu, Zn SODs have been isolated from a wide range of organisms, including yeast, spinach, chicken liver and bovine blood. In all these cases, a homodimeric enzyme is obtained, with a molecular weight of ~32,000 daltons and containing one Cu (II) and one Zn (II) per subunit. The subunits are stabilized by an intrachain disulfide bond, but associated by noncovalent forces. This enzyme requires Cu and Zn for its biological activity, and the loss of Cu results in its complete inactivation, leading in many cases to the development of human diseases [11]. Cu, Zn SOD has great physiological significance and therapeutic potential. The role of this enzyme has been investigated in various specific red blood cell (RBC) disorders, such as iron deficiency anemia, oxidative hemolytic anemia, thalassemia, sickle cell anemia, molecular dystrophy and cystic fibrosis, [12-15]. In recent studies, this enzyme has also been shown to be associated with dengue fever, postcholecystectomy pain syndrome, malign breast disease, steroid sensitive nephrotic syndorme and amyotrophic lateral sclerosis [16-18]. In rheumatoid arthritis, ischemic injury and cancer, SOD activity is considerably increased, suggesting a superoxide-related pathology and the involvement of SOD in these diseases. The principle aim of this article is to highlight the diseases associated with the expression of Cu, Zn SOD, as well as other superoxide dismutases.

DISEASES ASSOCIATED WITH CU, ZN SUPEROXIDE DISMUTASE

Prion diseases are characterized by neurodegeneration, gliosis and accumulation of extracellular deposits of the abnormal isoform of the prion protein (p_rP^{sc}), sometimes in the form of plaques. Human prion diseases include Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker Syndrome, and Fatal Familial Insomnia [19,20]. It has been confirmed that prion protein expression regulates Cu incorporation into Cu, Zn SOD, thereby modulating its activity. This reduces cellular resistance to oxidative stress and may regulate other copper-dependent aspects of cell metabolism. There is a strong link between Alzheimer's disease and the activity of superoxide dismutase. A study of several elements of the antioxidative system – Cu, Zn superoxide dismutase (SOD), catalase (CAT), the glutathione system (GLU), chemiluminescence (CHE), and antioxidant capacity (AOX) – was conducted in patients with dementia of the Alzheimer type (DAT) and vascular dementia (VD) [21]. A significant association was found between the antioxidant variables measured in blood samples taken from these patients, demonstrating that VD and DAT diseases are accompanied by oxidative disorders. In a different study, the activity of Cu, Zn SOD was determined in red blood cell (RBC) homogenate obtained from demented patients with DAT, from their first degree relatives, and from healthy, non-related controls [22]. A statistically significant increase in SOD activity was found in RBC homogenate between the families of DAT patients and controls. This increase probably represents a general alteration of the oxidative processes characteristic of this dementia, which supports the proposal that this enzyme could be used as a peripheral early diagnostic marker of Alzheimer's disease (AD). In an animal model of Alzheimer-like vascular pathology and inflammatory reaction, the possibility has been explored of deleterious vascular actions and inflammatory response to the cytokine tumor necrosis factor, interleukin-1, and amyloid-beta, as well as the protective effects of superoxide dismutase [23]. Zemlan et al. [24] have monitored the activity of Cu, Zn SOD in fibroblast cell lines derived from familial Alzheimer's patients and normal controls. Cu, Zn SOD activity was found to be significantly elevated in the patients, supporting the earlier theory that paired helical filaments are synthesized in Alzheimer's disease by free radical hydroxylation of proline residues in paired helical filament precursor protein.

In addition to all these findings, one remarkable study has described the localization of Cu, Zn SOD in the brain tissues of patients with Alzheimer's disease [25]. Immunostaining experiments showed that large pyramidal neurons, which are potentially susceptible to degenerative processes in AD, contain higher amounts of Cu, Zn SOD than other brain cells.

Recently, extensive work has been carried out on the link between amyotrophic lateral sclerosis (ALS) and SOD. ALS is a devastating neurological disease that rapidly progresses from mild motor symptoms to severe motor paralysis and premature death. Kruman et al [26] have employed a mouse model of ALS in order to test the excitotoxicity hypothesis of ALS. In this model overexpression of a mutant familial ALS–linked Cu, Zn SOD leads to progressive motor neuron (MN) loss and a clinical phenotype remarkably similar to that of human

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ALS patients. Under basal culture conditions, MNs in mixed spinal cord culture from the Cu, Zn SOD mutant mice exhibited enhanced oxyradical production, lipid peroxidation, increased intracellular calcium levels, decreased intramitochondrial calcium levels, and mitochondrial dysfunction. In an another study related to ALS, Vukosavic et al [27] have proposed that a mutation in the gene for Cu, Zn SOD, the only proven cause of ALS, induces the disease by a toxic property that promotes apoptosis. Further studies have been carried out in polypeptides of mutant Cu, Zn SOD in relation to ALS [28]. Ratovitski et al. [28] have shown that a mutation in the gene for Cu, Zn SOD causes a form of familial amyotrophic lateral sclerosis (FALS). In different kindreds, harboring different mutations, the duration of illness tends to be similar for a given mutation. For example, patients inheriting a substitution of valine for alanine at position 4 average a 1.5-year life expectancy after the onset of the symptoms, whereas patients harboring a substitution of arginine for histidine at position 46 (H46R) have an average 18-year life expectancy after disease onset. These studies show that 9 different FALS variants of SOD polypeptides appear to be soluble, but different mutant enzymes show a remarkable degree of variations with respect to activity, polypeptide half life, and resistance to proteolysis. Other studies related to ALS have confirmed that ALS is caused by a mutation in the gene for Cu, Zn SOD [29]. Transgenic mice expressing ALS-linked Cu, Zn SOD mutation exhibit a phenotype analogous to that of human ALS patients. In a recent study related to SOD and ALS [18], the aggregation of ubiquitin and a mutant ALS–linked Cu, Zn SOD protein correlates with disease progression and fragmentation of the Golgi apparatus (GA). In these studies, the transgenic mice that express the G93A mutation of human Cu, Zn SOD found in FALS showed the clinical symptoms and histopathological changes of sporadic ALS, including fragmentation of the neuronal GA. The finding of fragmented neuronal GA in asymptomatic mice, months before the onset of paralysis, suggests that the GA is an early target of the pathological processes causing neuronal degeneration. A subset of familial cases of ALS are linked to a missense mutation in the gene for Cu, Zn SOD [30]. Patients with such a missense mutation develop a paralytic disease indistinguishable from sporadic ALS, caused by the addition of an unknown function, which is toxic. Nitric oxide reacts with the superoxide anion to form the strong oxidant peroxynitrite, which is implicated in neuronal injury in a variety of model systems. Peroxynitrite is an alternate substrate for Cu, Zn SOD, causing catalytic nitration of its tyrosine residues in some patients. A mutation in the gene for Cu, Zn SOD may disrupt the active site of the enzyme and permit greater access of peroxynitrite to copper, leading to increased nitration by peroxynitrite of critical cellular targets. Kato et al [31] have characterized the neuronal Lewy body-like hyaline inclusions (LBHI) and astrocytic hyaline inclusions, which are the neuropathological markers of mutant SOD linked FALS.

The FALS mutations in the gene for Cu, Zn SOD are dominant, and are currently believed to exert their effects because of a gain of function rather than a loss of activity. The most convincing evidence for such a gain of toxic function is the observation that the expression of FALS mutant human Cu, Zn SODs in transgenic mice causes motor neuron disease, while expression of wild type (wt) human Cu, Zn SOD does not [32-34]. Knockout mice that do not express Cu, Zn SOD also do not develop motor neuron disease [35]. The gain of function hypothesis is also supported by the observation that expression of FALS mutant human Cu, Zn SOD is pro-apoptotic in cultured neuronal cells, while wt human Cu, Zn SOD is antiapoptotic [36]. The expression of the FALS mutant but not wt human Cu, Zn SOD in a human neuroblastoma cell line induced a loss of mitochondrial membrane potential and an increase in cytosolic calcium concentration [37]. It is also very likely that oxidative damage occurs as a result of the peroxidative activity of FALS mutant Cu, Zn SOD, and can be hypothesized to arise from either or both of the following two mechanisms. 1) increased access of the substrate to the active site, leading to increased oxidation of the substrate 2) increased formation of. OH radical due to the presence of Cu rather than Zn at the zinc site leading to a subpopulation of Cu, Cu-SOD that is more reactive. An intriguing third possibility is that increased production of. OH radicals could lead to damaged inactive mutant SOD enzyme, which could slowly release free Cu ions catalyzing deleterious Fenton-type oxidation reactions at or near the sites where they are released. In this regard, further work is needed to test the ability of a variety of hydroxyl radical scavengers to slow the inactivation of wt and mutant enzymes in their Cu, Cu and Cu, Zn forms by reaction with hydrogen peroxide.

Based on the studies by Jaarsma et al [38] related to Cu, Zn SOD and FALS, the observation has been made that one of the most puzzling aspects of SOD1-linked FALS is the large number of different mutations that yield mutants having a marked variability of biochemical/biophysical properties, but all causing a rather similar disease phenotype [39–42]. Studies so far have failed to identify a critical toxic property that links the different mutants to the disease [41,42]. This may indicate that this common toxic property arises either from a eitherto unrecognized function or property of the SOD1 Protein, or from multiple factors that contribute to the deleterious action of mutant SOD1s. Since SOD1 is both potentially dangerous (because of its capacity to bind Cu and Zn) and abundant, it is highly likely that abnormalities related to its synthesis or degradation could disturb cell function.

The role of Cu, Zn SOD in several other diseases has also been thoroughly studied. Plasma and total antioxidant status in patients with benign and malignant breast disease has been studied by Afrasyap et al [43]. The study was carried out on 25 women with breast cancer, 25 with fibrocystic breast disease, and 19 healthy subjects. Antioxidant enzyme activities and total antioxidant status were measured in the erythrocytes and plasma of patients and healthy individuals. A positive correlation was found between erythrocytes and plasma Cu, Zn

SOD activity in all groups, indicating that enzymatic and non-enzymatic antioxidants are differentially altered in human breast tumors. Superoxide dismutase activity has been determined by Gonzales et al [17] in RBC isolated from patients with acute myelogenous leukemia, chronic lymphocytic leukemia, Hodgkin's disease, lymphosarcoma and various visceral cancers. SOD activity was found to be significantly elevated in RBC from patients with acute myelogenous leukemia and lymphoproliferative syndromes. SOD activity levels further decrease with an increase in the duration of treatment. These results suggest an abnormality in the regulation of the expression of the SOD gene in the pluripotent stem cells. Built-in cellular defense mechanisms play a major role in tumor protection against non-surgical antineoplastic therapies. Of these, the overexpression of antioxidant enzymes such as SOD may be the most important [44].

The role of free radicals and Cu, Zn SOD has also been investigated in neuronal injury [45]. Free radicals may play an important role in several pathological conditions of the central nervous system (CNS), where they directly injure tissue, and where their formation may also be a consequence of tissue injury. Free radicals produce tissue damage through multiple mechanisms and can worsen acute neurodegenerative disorders including Parkinson's disease. These diseases are linked to a missence mutation of Cu, Zn SOD. A correlation between. OH radicals and Cu, Zn SOD activity in Parkinson's disease (PD) has also been suggested by the studies of Ihara et al [46]. The higher. OH level and lower Cu, Zn SOD activity may play a role in the onset of progression of PD, and pergolite may act neuroprotectively by inducing Cu, Zn SOD. In general, therapeutic approaches which limit oxidative stress may be potentially beneficial in several neurological diseases. Grasbon Frodl et al [47] have identified two polymorphisms of the MnSOD gene associated with Parkinson's disease. The Nobel Prize for physiology and medicine in 2000 was awarded for findings showing that Parkinson patients have abnormally low concentrations of dopamine in the basal ganglia [48]. As a consequence L-Dopa was developed, as a drug against Parkinson's Disease, and it remains to this day the most important treatment method for this disease.

Recent findings on the etiology of cataract and age-related muscular degeneration (AMD) suggest the role of an oxidative mechanism in these diseases [49]. In these studies high levels of erythrocyte SOD activity was associated with a two-fold increase in nuclear cataract.

Pitkanan and Robinson [50] have studied complex I (NADH– CoQ reductase) in patients with fatal infantile lactic acidosis (FILA), cardiomyopathy with cataract (CC), hepatopathy with tubulopathy (HT), Leigh's disease (LD), cataracts and developmental delay (CD) and lactic acidemia in the neonatal period followed by mild symptoms (MS). The production of superoxide radicals, in addition to NADH, was measured. Superoxide production rates were highest with CD and decreased in the order CD >> MS >LD >Control > HT > FILA = CC. The quantity of Mn superoxide dismutase (MnSOD) was highest in CC and FILA and lowest in CD. Given these observations, they hypothesized that oxygen radical production increases when complex I activity is compromised. Klaeger et al [51] have also confirmed that a higher level of Cu, Zn SOD can reduce the severity of oxygen-induced retinopathy in a mouse model.

The diseases associated with dengue fever include the classical dengue (DEN), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). SOD and other antioxidant proteins have been found to be abnormal in these diseases [16]. The preliminary report of dengue confirms the assumption of free radical generation and alteration in antioxidant status during acute illness. However, further studies are required to understand their complex interaction in disease progression and the possible therapeutic utility of the findings. Changes in Cu, Zn SOD activity have also been found in children with steroid-sensitive nephrotic syndrome (NS), implicating the role of free radicals in the development of this syndrome [52]. Erythrocyte antioxidant activity and trace element levels are also the best markers in Behcet's disease [53]. Selenium (Se), Zinc (Zn), Copper (Cu) and antioxidant enzymes, including SOD levels in sera, have been detected in Behcet patients. In this study, the SOD level was low in the serum of Behcet's disease patients. It has been suggested that decreased SOD activity and increased production of free oxygen radicals may play a role in the etiopathogenesis of this disease.

Antioxidant enzyme activity, especially Cu, Zn and Mn SOD, has also been studied in human abdominal aortic aneurysmal and occlusive diseases [54]. The activity of these enzymes was lowered in the tissue of these patients, which points to the involvement of free radicals. The plasma extracellular SOD levels in an Australian population with coronary artery disease were measured [55]. The results of these studies show an association between extracellular SOD (EC-SOD) and coronary artery disease. EC-SOD is considered to be more protective, contributing to reduced coronary risk. Down's syndrome (DS), which is characterized by premature aging, has also been related to oxidative stress, resulting from the aberrant expression of Cu, Zn SOD [56]. SOD activity has also been measured in the blood of different individuals between 50 to 93 years of age and the level of this important enzyme was found to decrease with age [57]. In diabetes, the persistence of hyperglycemia has been reported to cause increased production of oxygen free radicals through glucose autooxidation and nonenzymatic glycation. The highest erythrocyte SOD activity has been found in diabetic children at the onset of clinical diabetes. In diabetic adolescents, SOD activity is also significantly higher than in control subjects. Decreased antioxidant defenses may increase the susceptibility of diabetic patients to oxidative injury. Appropriate support for enhancing antioxidant supply in these young diabetic patients may help in preventing clinical complications during the course of the disease [58].

There are other diseases that have close association with SOD, but our goal in this article is to focus on the most recent literature available related to those diseases discussed in the previous section. Studies on SOD in biological systems and the deleterious effect of the O_2 generating system on biological macromolecules, subcellular components, cells and tissues suggest that O_2 can be an initiating or contributing factor in most of these diseases. Superoxide-related pathology may result either from increased production of O_2 due to hyperoxia, activation of granulocytes and macrophages, conversion of xanthine dehydrogenase to xanthine oxidase, exposure to ionizing radiation and redox cycling of xenobiotics, or from decreased activity of SOD.

THERAPEUTIC POTENTIAL

Keeping in mind the association of SOD with so many diseases, it is equally important to highlight its therapeutic potential. SOD can be used in mustard gas (MS) burns [59]. MS has been used in chemical warfare since World War I. The blistering skin lesions are slow to heal. Secondary inflammation, as well as damage to organs distant from the original wound, can occur due to these burns. Presently there is no antidote for burns and poisoning by MS. A study by Eldad et al (59) has shown that treatment modalities with free oxygen radical scavengers, Cu, Zn and Mn SOD are effective for MS skin burns in an experimental guinea pig model. Each of the SOD compounds dramatically reduced the burn lesion area when administered intraperitoneally / intralesionally (i. p/i. l) before wound infliction. Studies conducted by Danel et al [60] have confirmed that gene therapy for oxidant injury-related diseases can be used to overcome oxidant injury by augmenting intercellular antioxidant enzymes. When adult rats were injected intratracheally with an adenovirus (Ad) vector encoding human Cu, Zn SOD or catalase cDNA, a mixture of both Ad vectors or a control Ad vector containing no exogenous gene, the expression of human catalase and Cu, Zn SOD was demonstrated 3 days later in distal lung epithelial cells and alveolar macrophages. After exposure to 100% O_2 for 62 hrs, survival was greater in rats injected with catalase and/or SOD Ad vectors than in control rats. A clinical trial has been performed for successful treatment of radiation-induced fibrosis using liposomal Cu, Zn SOD [61].

Koksoy et al [62] tried to compare the prophylactic effects of SOD, SOD + catalase, desferrioxamine, verapamil and disulfiram, all free oxygen radical scavengers, in an animal model of experimental acetic acid colitis. The positive effect of SOD on the recovery of human hemopoietic stem cells has been successfully shown by Ma et al. [63]. Their study demonstrated that the addition of SOD to hypothermic storage media may increase the recovery of hemopoietic stem cells.

CONCLUSION

From the literature available to date it is evident that free radical processes and the biological defenses against them are an important area of the biological response to various diseases. The functional status of SOD1 could be considered a reliable index of the ability of the organism to withstand various pathological conditions. The full significance of SOD in the diagnosis and prophylaxis of various disease conditions is among the most crucial areas in modern biomedical and environmental research.

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